II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 67 and 86-89 were pending prior to the Office Action dated June 10, 2004.

B. Claims Are Adequately Described

The Action rejects claims 67 and 86-89 as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Action argues that the claims contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Paper No. 19 at page 5. The Action also contends that the instant specification does not contemplate adenoviral vectors comprising a wild type p53 gene operably linked to a promoter or to a promoter that is a CMV, RSV, β-actin or SV40 promoter. Action at page 2. It concludes that the application is given a priority date of November 23, 1999—the date on which the instant application was filed. Applicant respectfully traverses this rejection.

As discussed in previous filings, the present specification adequately describes the invention to fulfill the written description requirement. The written description requirement is whether the "description clearly allows persons of ordinary skill in the art to recognize that he or she invented what is claimed." MPEP 2163.02 (citing *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989)). Applicant contends that it is clear that the specification describes what is claimed in rejected claims 67, 86-89. The claims are generally directed to an "adenovirus vector comprising a wild type p53 gene under the control of a promoter." The written description of this application supports this claim and claims 67 and 87-

89, which recite specific promoters. The specification makes clear that the inventor was in possession of the claimed invention:

- "In one specific embodiment, the invention concerns vector constructs for introducing wild type p53 genes (wt-*p53*) into affected target cells suspected of having mutant *p53* genes. These embodiments involve the preparation of a gene expression unit wherein the wt-*p53* gene is placed under the control of the β-actin promoter, and the unit is positioned in a reverse orientation into a retroviral vector." Specification at page 9, lines 6-12.

- In Example III, "The *p53* cDNA with its β-actin promoter was cloned into the LNSX retroviral vectors in ***both*** orientations." Specification at page 61, lines 29-30 (emphasis added).

- "While this affect [sic] was observed using the β-actin promoter and a retroviral expression vector, the inventors believe that this phenomenon ***will be applicable to other promoter/vector constructs for application in gene therapy***." Specification at page 8, line 25 to page 9, line 4 (emphasis added).

- "In addition to retroviruses, it is contemplated that ***other vectors can be employed, including adenovirus***...." Specification at page 14, lines 21-23 (emphasis added).

- "By way of illustration, but not limitation, one can mention the following bectors, including N2A, LN, LNSX, Adenovirus and Adeno-associated virus." Specification at page 33, lines 9-11.

- "While the **β-actin promoter** is preferred, the invention is by no means limited to this promoter and one may also mention by way of example promoters derived from **RSV**, N2A, LN, LNSX, LNSN, **SV40**, LNCX or **CMV**." Specification at page 15, lines 1-4 (citations omitted) (emphasis added).

- "***Generally speaking***, such a promoter might include either a human cellular or viral promoter. While the β-actin promoter is preferred the invention is by no means limited to this promoter...." Specification at page 14, line 35-page 15, lines 2 (emphasis added).

- "While the retroviral construct aspect of the invention concerns the use of a β-actin promoter in reverse orientation, there is no limitation on the nature of the selected gene which one desires to have expressed. Thus, the invention concerns the use of antisense-encoding constructs ***as well as 'sense' constructs that encode a desired protein.***" Specification at page 16, lines 5-10.

Therefore, the specification *as a whole* makes clear that 1) p53 sense constructs are contemplated in both orientations; 2) any discussion about antisense constructs applies to "sense" constructs such as p53; 3) constructs can be retroviral, but they may also be adenovirus constructs, and thus, are not limited to retroviruses; 4) promoters are discussed both generally and in the context of antisense constructs, in addition to CMV, RSV, and SV40 being specifically mentioned; and finally, 5) because an adenovirus can be used instead of retrovirus and since constructs are not limited to antisense constructs, applying equally to sense constructs, there is adequate written description for an "adenovirus vector comprising a wild type p53 gene under the control of a promoter," as well as for vectors with a CMV promoter.

The Action goes through each citation individually to argue that there is no written description for the claimed invention. However, the issue is whether the disclosure as a whole indicates that Applicant was in possession of the invention. As shown above, the skilled artisan would recognize that embodiments discussed in the application could be practiced in the context of a pharmaceutical composition of adenovirus and with the recited promoters to express a wild type p53 gene. Therefore, as a whole, the application supports the claimed invention.

In addition to the Declaration of Dr. Lou Zumstein, submitted with the Response filed on October 18, 2001, Applicant submitted the Declaration of Dr. Philip Hinds with the CPA filed on May 13, 2002. Both of these constitute evidence from a person of ordinary skill in the art to support the contention that the Applicant was in possession of the claimed invention at the time the priority application was filed. Applicant contends that the Action has not rebutted the evidence submitted by persons of ordinary skill in the art to maintain the rejection of these claims. Such evidence meets the "preponderance of the evidence" standard set forth in MPEP § 2163.04. The declarations and the identified portions of the specification show the written

description requirement has been met. Accordingly, Applicant respectfully requests this rejection be withdrawn.

The Action contends that in the places where adenovirus or promoters claimed are disclosed, "each such disclosure is within the context of antisense RNA production." Office Action page 6. Applicant denies that adenoviruses are discussed in the application only in the context of antisense embodiments. The paragraph in which the Specification discloses that other vectors such as adenovirus can be used instead of a retrovirus begins, "In broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors which incorporate nucleic acid sequences encoding the desired construct, once introduced into the cell to be treated...." Specification at page 14, lines 9-12. The use of adenovirus is discusses in the context of "broader aspects of the invention," and retroviruses and antisense constructs are but examples of aspects of the invention. Similarly, as quoted above, the following paragraph discussing promoters indeed recites particular embodiments of the invention, such as antisense; however, it says, "***Generally speaking***, such a promoter might include either a human cellular or viral promoter. While the β-actin promoter is preferred the invention is by no means limited to this promoter...." Specification at page 14, line 35-page 15, lines 2 (emphasis added).

Because the Specification indicates to a skilled artisan that the inventor was in possession of the claimed invention at the time the application was filed, Applicant respectfully requests this rejection be withdrawn. Furthermore, because the application complies with 35 U.S.C. §112, the claims are entitled to the benefit of their priority date of October 13, 1992. 35 U.S.C. 120.

C. Claims 67 and 86 Are Not Anticipated under § 102 (b)

The Action rejects claims 67 and 86 as unpatentable over Liu *et al.* (1994) ("Liu") based on 35 U.S.C. § 102(b). It contends that Liu anticipates the claimed invention. Applicant respectfully traverse this rejection.

As discussed above, the present application is entitled to claim priority to U.S. Application ('513 application), filed October 13, 1992. Accordingly, claims 67 and 86 are not anticipated by Liu because it is not prior art against the claimed invention. Liu was published in 1994, while the present application is entitled to a priority date that precedes the Liu publication date. Because Liu is not prior art against the application, it cannot anticipate the claimed invention. Consequently, Applicant respectfully requests this rejection be withdrawn.

D. Claims 86-89 Are Not Obvious

The Action rejects claims 86-89 as obvious over the references of Chen *et al.* (1990) ("Chen reference") and Stratford-Perricaudet *et al.*. *Human Gene Therapy* 1, 241-256 (1990) ("Stratford-Perricaudet reference") in view of Wilkinson *et al.* (Wilkinson), Colicos *et al.* (Colicos), Rajan *et al.* (Rajan), and Hitt *et al.* (Hitt). Applicant respectfully traverses this rejection.

Applicant specifically incorporates by reference each of the responses to Office Actions previously filed in this case. In addition, Applicant provides the following arguments.

1. The claimed invention produced surprising and unexpected results

The claimed invention is directed to particular pharmaceutical compositions of adenoviral vector compositions comprising p53 in the context of gene therapy. As argued earlier, the PTO has widely espoused the view that gene therapy is an unpredictable area. Applicant previously provided a statement from Examiner Guzo in a case related by priority to the present application (USN 08/459,713) and a declaration from Deborah R. Wilson, both showing that the claimed invention achieves the surprising and unexpected result of clinical efficacy.[1] By the PTO's own admission, that any gene therapy is successful constitutes a surprising and unexpected result that

could not have been predicted based on the prior art cited in this case. The prior art does not provide evidence of clinical efficacy and instead merely provides basic tools that the skilled artisan is expected to combine to create the claimed invention. Because the claims recite a pharmaceutical composition, they are directed to clinical applications.

The clinical evidence previously filed demonstrates the therapeutic value of adenovirus p53 compositions, which could not have been predicted based on the cited prior art. As such, this is additional evidence to rebut the contention that the claimed invention is obvious.

2. Issued and Allowed Claims Concerning Ad-p53

Applicant previously provided a list of several patents and pending, but allowed, patent applications that involve adenovirus vectors expressing p53. These patents and patent applications claim priority to the same application for which priority is claimed in the present application.

This list has been updated in Table 1 below (copies were previously provided).

Table 1

1) U.S. Pat. No. 6,410,010
2) U.S. Pat. No. 6,511,847
3) U.S. Pat. No. 6,143,290 (same Examiner as present case)
4) U.S. Serial No. 08/626,678
5) U.S. Serial No. 08/459,713 (now U.S. Patent 6,740,320)
6) U.S. Serial No. 09/413,109

This list is further evidence that the claimed invention is novel and nonobvious over the cited prior art. The Action contends that none of the issued claims are to adenoviral vectors where a p53 gene is operably linked to a β-actin, RSV or SV40 promoter and that some of the claims are to methods of treatment. Applicant contends that the methods of treatment claims are relevant to

[1] The Declaration of Dr. Lou Zumstein is provided to show that INGN 201 (marketed as "Advexin®" by Introgen Therapeutics, Inc.) is the same Ad-p53 vector disclosed in the Examples of USN 08/145,826 (now U.S. Patent No. 6,410,010), to which all of the cited patents in Table 1 claim priority (Appendix G).

the claims at issue because of the position the PTO has taken, which Applicant does not state he agrees or does not agree with, during the prosecution of these patents and patent applications. Applicant understands that the PTO has essentially indicated that nonpharmaceutical composition claims are patentably distinct from pharmaceutical composition claims and that pharmaceutical composition claims are not patentably distinct from methods of using such compositions to treat a subject. This is in contrast to the position taken by the Examiner in this case.

a) Prosecution of USN 08/459,713 (now U.S. Patent 6,740,320)

A general summary of the prosecution of a related case as it pertains to pharmaceutical claims is as follows: method claims in Application A were rejected under obviousness-type double patenting over pharmaceutical composition claims, and not the non-pharmaceutical composition claims, in Application B. Applicants removed the pharmaceutical claims forming the basis for the rejection from Application B and added them to Application A. The examiner went on the record saying that the pharmaceutical composition claims were distinguishable from the composition claims because only the pharmaceutical claims rendered the method claims obvious. Moreover, a Restriction Requirement that issued early in a parent application to the patents and applications in Table 1 generally set forth that the method claims were a different invention from the composition claims. Appendix A; Restriction Requirement in parent application.

More specifically, during the prosecution of U.S. Application Serial No. 08/459,713 ("the '713 application"), method claims in the '713 application (generally directed to methods of treating cancer with adenovirus comprising wild-type p53) were rejected under a provisional non-obviousness-type double-patenting rejection (Appendix B: Office Action dated January 4, 2001 (Paper 25)). The rejection of the method claims was based on claims 29-32 and 34-35 of

co-pending and related application 08/626,678 (INRP:005--1) ("the '678 application"). Claims 29-32 and 34-35 of the '678 application were pharmaceutical composition claims (Appendix C). The January 4, 2001 Action in the '713 patent application stated that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the '678 application recite pharmaceutical compositions comprising recombinant adenoviral vectors capable of expressing the p53 gene, wherein said pharmaceutical compositions are designed to be administered to humans for treatment of cancer (as per the instant claims)." Page 7. In other words, the examiner in the '713 case went on record as saying that Ad-p53 pharmaceutical composition claims and methods of treatment claims using Ad-p53 were not "patentably distinct." Applicant notes that this is not a statement regarding search burdens but an affirmative statement regarding what is "PATENTABLE (novel and nonobvious) over each other." *See* MPEP § 803 (defining what "distinct" means).

Applicants responded to the January 4, 2001 Office Action saying that the rejections were provisional and that the substance of the rejections would not be addressed at that time.

Similarly, in the prosecution of the '678 application, the method claims of the present case were cited in a provisional obviousness-type double-patenting rejection of the pharmaceutical composition claims. (Appendix D: Office Action dated July 11, 2001 (Paper 21)). That Office Action stated: " It would have been obvious for the ordinary skilled artisan to use the instantly claimed pharmaceutical compositions in the methods of treated cancers recited in the '713 application because said pharmaceutical compositions are designed to treat cancer by introducing normal p53 coding regions to cancer cells which lack a normal p53 gene." Pages 5-6.

In response to the July 11, 2001 Office Action in the '678 case, Applicants traversed the provisional obviousness-type double-patenting rejection (Appendix E: Response to Office Action dated July 11, 2001). They argued the double-patenting rejection was inappropriate because a restriction requirement had been sent out by the Patent Office in the parent application (08/145,826) in which the adenoviral composition claims were restricted from the treatment method claims (Appendix A: Restriction Requirement). In the subsequent Office Action, however, the Action indicated this argument was not persuasive (Appendix F: Office Action dated January 3, 2002 (Paper 24)). It stated that the basis for the rejection was not the adenoviral composition claims, but specifically the pharmaceutical composition claims. It further said: "Clearly, the instantly claimed pharmaceutical compositions comprising recombinant adenoviruses capable of expressing wild-type p53 are obvious over claims (pending in the '713 application) reading on a method of treating cancers in patients comprising administering pharmaceutical compositions comprising recombinant adenoviruses capable of expressing wild-type p53 because the method claims (in the '713 application) merely recite the intended use of the instantly claimed pharmaceutical compositions." Page 7.

While the claims in the '678 application were eventually allowed, the reason for the allowance was that the double-patenting rejections were all provisional. Applicants subsequently canceled the pharmaceutical composition claims in the '678 application and filed a continuation application because of the Patent Office's position.

Meanwhile, Applicants filed claims 75-101, which are directed to pharmaceutical compositions, in the '713 application. Applicants reasoned that this was appropriate as a result of the Patent Office's double-patenting position in this case and the '678 application. Some of the added claims are nearly identical in scope to the claims canceled in the '678 application.

Furthermore, even if some of the claims were of a different scope, nothing in the Office Actions concerning the double-patent rejections would indicate that the scope can be the basis for distinguishing the pharmaceutical composition claims from the method of treatment claims as a separately patentable invention. As indicated in the Office Actions of these other cases (Appendices D and F), the Patent Office's opinion was that pharmaceutical compositions comprising recombinant adenoviruses capable of expressing wild-type p53 are not patentably distinct with respect to methods of treating cancers in patients comprising administering recombinant adenoviruses capable of expressing wild-type p53. Consequently, Examiner Guzo permitted claims 75-101 to be added into the '713 application and he subsequently allowed the case.

b) Relevance to Current Application

The present Action generally takes the position that a "pharmaceutical composition" claim is similar to a composition claim and that "[i]t is the products, the pharmaceutical compositions comprising adenovirus, that is claimed; not the methods of gene therapy." Action at page 12. This is in marked contrast to the previous position upheld by the PTO, that pharmaceutical composition claims were distinct from non-pharmaceutical composition claims because only the former were obvious over methods claims, while the latter were patentably distinct from method claims. It is inconsistent and, thus, improper for the PTO to now to take this new position. Moreover, Applicant points out the fundamental unfairness of switching positions at this point, particularly given Applicant's reliance on the PTO's stance in earlier prosecutions. These issues could significantly affect patent term and the validity of **issued patents** and allowed patent applications. Because patents have already issued, Applicant urges that the position in this case be made consistent with the position that the PTO has previously taken with respect to those issued and allowed patents, particularly that pharmaceutical composition claims are patentably

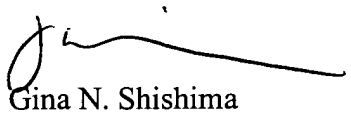
distinct from non-pharmaceutical composition claims and that evidence of clinical efficacy is merits a conclusion of nonobviousness with respect to the pharmaceutical composition claims.

CONCLUSION

Applicant believes that the foregoing remarks fully respond to all outstanding matters for this application. Applicant respectfully requests that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



Gina N. Shishima
Reg. No. 45,104
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: December 10, 2004

APPENDIX "A"

AUSTIN KIT UTSC:350

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/145,826	10/29/93	ZHANG W	UTSC:350

GUZO, D EXAMINER

18N2/0603

BARBARA S. KITCHELL
ARNOLD WHITE & DURKEE
P.O. BOX 4433
HOUSTON, TX 77210

ART UNIT	PAPER NUMBER
1805	10

DATE MAILED: 06/03/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire Three (3) month(s), ~~_____ days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449. (2)
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-21 are pending in the application.
   Of the above, claims 9-21 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-8 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other Response

DOCKETED
FOR 9-3-94
BY Cru
CHK'D. BY _____

P19909
COMPUTER INPUT #

REC'D A.W. & D.
JUN 07 1994
DOCKET DESK

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

1. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-8, drawn to recombinant adenoviruses, classified in Class 435, subclass 320.1.
II. Claims 9-13, drawn to a method of restoring p53 function, classified in Class 424, subclass 93T.
2. III. Claims 14-21, drawn to a method of making recombinant adenoviruses, classified in Class 435, subclass 172.3.
3. This application contains claims directed to the following patentably distinct species of the claimed invention: Applicants claim host cells, in vitro or in vivo, infected with recombinant adenoviruses capable of expressing p53. A further election of one of these two species with any of elected Groups I-III is further required under 35 USC 121.

Host cells *in vivo* which are infected with the instant adenovirus vectors containing the p53 gene read on a patentably distinct product resulting from a use of the instant invention as a therapeutic agent while host cells *in vitro* which are infected with the instant vectors read on a patentably distinct product resulting from the use of the instant vector as an expression system. A reference anticipating one type of host cell would not have rendered the other obvious.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

The inventions are distinct, each from the other because of the following reasons:

4. Inventions I and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the adenoviruses of Group I could have been constructed by

restriction endonuclease digestion and direct in vitro ligation of foreign DNAs into the adenovirus genome.

5. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the adenoviruses of Group I could have been used as an expression system for production of recombinant proteins in cells in vitro.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter restriction for examination purposes as indicated is proper.

7. During a telephone conversation with Barbara S. Kitchell on 03/22/94 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-8 with the species of Claim 8 reading on cells in vitro. Affirmation of this election must be made by applicant in responding to this Office action. Claims 9-21 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

As noted above, *in vitro* and *in vivo* host cells are patentably distinct concepts and co-claiming thereof in a single claim is the basis for restriction. Accordingly, the generic claim has been examined only to the extent that it reads on the elected species.

It is noted that the claimed invention was not described in the parent application (S.N. 07/960,513) and therefore the effective priority date for the claimed invention is the filing date of the instant application (10/29/93).

9. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because:
The Serial Number for the parent application for which benefit was claimed under 35 USC 120 is incorrect. The correct S.N. should be 07/960,513.

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

11. Claims 1-8 are rejected under 35 U.S.C. § 103 as being unpatentable over Srivastava in view of Casey et al., Gomex-Foix et al. and Stratford-Perricaudet et al.

Applicants have recited a recombinant adenovirus vector (with the E1A and E1B regions deleted) comprising the p53 tumor suppressor gene operably linked to the CMV IE promoter and SV40 early polyadenylation signal (polyA signal) and a host cell infected with said virus.

Srivastava (U.S. Patent #5,252,479, issued 10/12/93, filed 11/08/91, See whole document, particularly Column 6, 2nd paragraph and Claim 9) recited the generation of adeno-associated virus (AAV) vectors comprising the p53 gene and use of said vectors (in pharmaceutically acceptable carriers) to transduce said p53 gene into host cells. Srivastava did not recite the generation of recombinant adenovirus vectors comprising the p53 gene.

Casey et al. (C20, See whole document, particularly the Abstract and page 1791, first 3 paragraphs) recited the tumor suppressor activity of the p53 gene product and the possibility that introduction of the p53 gene into cells may function to suppress growth of some cancer cells.

Gomez-Foix et al. (C21, See whole article, particularly the Methods and Materials Section, first 2 paragraphs) recited the generation of recombinant adenoviruses comprising operably linking the CMV IE promoter/enhancer sequence and SV40 poly(A) signal to the foreign gene to be expressed.

Stratford-Perricaudet et al. (C31, See whole article, particularly page 54) recited an overview of the art concerning the generation of recombinant adenovirus vectors and the dispensibility of the E1A and E1B regions in said vectors.

Applicants invention is the generation of recombinant adenovirus vectors comprising the tumor suppressor p53 gene. Said vectors were useful for transducing the p53 gene into cells as a method for potentially inhibiting tumor growth. The key

question to be answered in the present case is therefore whether it would have been obvious to clone the p53 gene into an adenovirus vector. For the following reasons, the answer must be considered yes. First, the p53 gene had been shown to encode a protein believed to have tumor suppressor activity in some cells (Casey et al.) and the ordinary skilled artisan would have been motivated to introduce this gene into target cells in hopes of inhibiting tumor growth. Second, Srivastava had used AAV vectors to transduce the p53 gene into target cells and had therefore provided evidence to indicate that the p53 gene could be transferred to cells by a recombinant viral vector. The question to be asked at this point is whether the ordinary skilled artisan, seeking to vector the p53 gene into target cells, would have been motivated to use an adenovirus vector instead of an AAV vector. The answer must again be yes because adenovirus vectors offered several distinct advantages over other vectors; specifically, Stratford-Perricaudet et al. indicated that "The potential for this virus to accommodate a large piece of DNA and to express a gene in the absence of both viral and cellular replication make this virus an attractive gene transfer system." Page 51, Abstract) and that "it may prove realistic to use such a vector to target any organ in vivo." (Page 58, 1st paragraph). With regard to the specifics of the vector construction (i.e. the use of the strong CMV IE promoter and SV40 poly(A) signal to drive proper expression of the p53 gene), Gomez-Foix et al. specifically recited the construction of adenovirus vectors

comprising operably linking the foreign gene to be expressed to the CMV IE promoter/enhancer and the SV40 poly(A) signal sequences. It is also noted that the CMV IE promoter/enhancer and SV40 poly(A) sequences were among the most commonly used sequences in the construction of many different types of viral vectors and were used, in the instant invention, for their known and expected gene expression regulatory properties. Therefore, given the many desirable attributes of adenovirus vectors for transducing genes of interest into target host cells, given the well known methods for generating said vectors and given the prior art teachings on the p53 tumor suppressor gene, it must be considered that it would have been obvious to the ordinary skilled artisan, seeking to introduce the p53 gene into target host cells, to clone said gene into an adenovirus vector. Given the well known and successful teachings on the generation of recombinant adenoviral vectors capable of transducing and expressing a foreign gene of interest, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in producing a recombinant adenovirus vector comprising the p53 gene.

12. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use

the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-8 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the instantly disclosed adenovirus (Ad5 derived) vectors and host cells capable of being infected with said vectors. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Applicants' claims read broadly on any adenovirus engineered to contain the p53 gene. It is also noted that generation of the instant adenoviruses requires generation of complementing cell lines capable of expressing the essential viral genetic function(s) deleted from the adenovirus. Therefore, to enable the invention for the 42 different known adenovirus serotypes or subgroups A-F, the skilled artisan would have needed to characterize the genomes of said viruses (many were poorly characterized), determine the essential viral genes, generate complementing cell lines transformed to constitutively express the essential viral protein(s), determine if the complementing cell lines could express the viral protein at levels sufficient to allow for the generation of usable numbers of recombinant viruses, determine if the replication defective recombinant adenoviruses could have infected target host cells and expressed the p53 gene in said cells, etc. Indeed, applicants indicated that the Ad5 virus was disclosed as the only embodiment in the instant application "...because Adenovirus 5 is a human adenovirus about which there is significant amount of biochemical

and genetic information known, and which has historically been used for most constructions employing adenovirus as a vector." Therefore, it must be considered that the ordinary skilled artisan, seeking to enable the full scope of the instant invention, would have had to practice a degree of experimentation which would not have been routine but which would have instead involved numerous new scientific discoveries concerning the more poorly characterized adenoviruses and would have been undue and excessive.

It is further noted that the courts have held, in cases involving unpredictable factors (the expression vector art certainly qualifies here!), that the scope of enablement varies inversely with the degree of unpredictability of the factors involved and that the scope of the claims must bear a reasonable correlation, in the view of persons of ordinary skill in the art to which the invention pertains, to the scope of enablement provided by the specification.

It is noted that the references listed on the PTOL-1449 filed 04/18/94 and 24 of the references listed on the PTOL-1449 filed 04/12/94 have not been received by this Office and hence have not been considered by the Examiner.

No claims are currently allowable in this application.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1.

The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (Nov. 16, 1993) and 1157 OG 94 (Dec. 28, 1993) (See 37 CFR 1.6(d)). The CM1 Fax Center number is (703) 305-3014. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid processing of duplicate papers in the Office.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906.

David Guzo
June 1, 1994

RICHARD A. SCHWARTZ
SUPERVISORY PATENT EXAMINER
ART UNIT 185

APPENDIX "B"

INRP:019
HYL (CAUS)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/459,713	06/02/95	ZHANG W	UTSC.466/HYL

HM12/0104

ARNOLD WHITE AND DURKEE
P O BOX 4433
HOUSTON TX 77210

EXAMINER	
GUZO,D	
ART UNIT	**PAPER NUMBER**
1636	25

DATE MAILED: 01/04/01

REC'D HOWREY SIMON ARNOLD & WHITE

JAN 0 8 2001

HOUSTON DOCKETING DEPT.

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

RECEIVED
Date(s) Docketed: 4/4/01 Resp. to Office; 7/4/01 Final deadline.

JAN 1 9 2001

Client: INRP:019
Attorney(s): HYL
Initials: KM 1099

Office Action Summary

Application No.	Applicant(s)
08/459,713	Zhang et al.
Examiner	**Group Art Unit**
David Guzo	1636

☒ Responsive to communication(s) filed on *Sep 15, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

DOCKETED ☐ UPDATED ☐
Previously ___ Not Required ✓
Appl. Info ___
Reg/Grant Info ___
Action Required: ___
TRANSFERRED
Date Due/Docket: ___
By: JM Checked ___

☒ Claim(s) *9-13 and 24-72* is/are pending in the applicat

Of the above, claim(s) ___ is/are withdrawn from consideration

☐ Claim(s) ___ is/are allowed.

☒ Claim(s) *9-13 and 24-72* is/are rejected.

☐ Claim(s) ___ is/are objected to.

☐ Claims ___ are subject to restriction or election requirement.

FINORCHIO & SANORSKI

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on ___ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on ___ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

REC'D HOWREY SIMON ARNOLD & WHITE
REC'D HOWREY SIMON ARNOLD & WHITE
JAN
JAN 0 8 2001
HOUSTON
HOUSTON DOCKETING DEPT.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) ___.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: ___

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *24*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicants' request that the computer readable form of the Sequence Listing filed in the parent application 08/145,826 be used to prepare a file for the instant case is acknowledged. A Sequence Listing for this application will be prepared.

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 9-13 and 24-26 and 28-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating cancers comprising administration of the Ad5CMV-p53 recombinant adenovirus, does not reasonably provide enablement for treating any cancers comprising using any adenovirus comprising the p53 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with the information known in the art without undue experimentation (United States v. Teletronics Inc. 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based upon a single factor, but rather a conclusion reached by weighing many factors. These factors are outlined in *Ex parte Forman* 230

USPQ 546 (Bd. Pat. App. & Inter. 1986) and in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and they include the following:

1) Unpredictability of the art. The gene therapy art is extremely unpredictable. Often the ability of a vector to express a therapeutic transgene in cells *in vivo* is dependent upon the specific vector chosen, the vector design, the promoter used to derive expression of the transgene, the method of delivering the vector to the target cells, etc. (See Fox, Nature Biotechnology, 2000, Vol. 18, pp. 143-144; Kmiec, American Scientist, 1999, Vol. 87, pp. 240-147; Anderson, Nature, 1998, Vol. 392, pp. 25-30; Verma et al., Nature, 1997, Vol. 389, pp. 239-242; Ross et al., Human Gene Therapy, 1996, Vol. 7, pp. 1781-1790, etc.). Given the unpredictable behavior of gene therapy vectors *in vivo* and given the many failures in gene therapy, it is impossible to predict, *a priori*, the *in vivo* characteristics of gene therapy vectors and whether said vectors will have any therapeutic effects in patients.

2) State of the art. The state of the art at the time of applicants' invention was nil with no examples of successful treatment of human cancers using adenoviral (or any other) vectors.

3) Amount of guidance provided by applicants. The only vector exemplified in the instant specification and the only vector which possesses the recited *in vivo* activities is the Ad5CMV-p53 vector. The Ad5CMV-p53 vector is a "first generation" adenoviral vector containing a deletion of the E1a and E1b regions and substitution of an expression cassette for said deleted region. However, the claims encompass second generation adenoviral vectors which are not disclosed in the specification (i.e. no working examples are described), wherein the procedures

which would be used to generate said vectors are not disclosed (i.e. what packaging cell lines would be necessary to package these vectors, what procedures would be used to delete portions of the E3, E4, etc. genes, what portions of the E3, E4, E2, etc. genes would need to be deleted, etc.). Indeed, development of second generation adenoviral vectors as claimed by applicants (i.e. involving deletion of the E4 gene, E2 gene, etc.) did not occur until after the effective filing date of applicants' invention (see, for example, the review by Wang et al., Nature Medicine, 1996, Vol. 2, No. 6, pp. 714-716). Applicants' specification provides no guidance on how the skilled artisan would generate these second generation adenoviral vectors and only recites that other adenoviral genes can be deleted and serve as potential insertion sites for expression cassettes. These teachings are essential for practicing the claimed invention and must be included in the specification. Assertions that the skilled artisan would have been able to provide the missing teachings cannot compensate for a lack of an enabling disclosure (See *Genentech v. Novo Nordisk A/S*, 42 USPQ2d 1000, 1997).

4) Number of working examples. Applicants' only working example is the Ad5CMV-p53 vector.

5) Scope of the invention. The invention is broad with the broadest claims reading on use of any adenoviral vector comprising the p53 gene inserted at any genomic location in the adenovirus.

6) Nature of the invention. The invention involves one of the most complex and unpredictable aspects of molecular biology/medicine; gene therapy using recombinant viral (adenoviral) vectors.

7) Level of skill in the art. The level of skill in the gene therapy art is high; however, as noted by

some of the most prominent gene therapy researchers (i.e. W. French Anderson, Verma, etc.), the level of unpredictability in this poorly developed art is high.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 9-13, 22-52 and 56-72 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-97 of copending Application No. 09/413,109 (hereafter the '109 application) in view of Berkner. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the '109 application recite the same methods for treating human cancer patients comprising administering pharmaceutical compositions comprising

adenoviral vectors containing the p53 gene. The claims in the instant application differ in that they recite use of adenoviral vectors comprising expression cassettes for expression of the p53 gene (i.e. use of a promoter such as SV40, SV40 polyA signal), deletion of the E1 region and substitution of the p53 gene therein, and use of an origin of replication (i.e. from adenovirus). However, Berkner (Current Topics in Microbiology and Immunology, 1992, Vol. 158, pp. 39-66, see whole article, particularly Fig 2(a) and (b), pp. 43, 52, 54 and 59) teaches construction of adenoviral vectors comprising deletions of the E1 region and substitution of a heterologous expression cassette therein, use of the SV40 promoter and polyA sites to direct expression of heterologous genes in adenoviral vectors and use of an origin of replication in the vectors to facilitate replication of the vectors. Therefore, the ordinary skilled artisan would have been motivated to generate and use replicating adenoviral vectors comprising deletions in the E1 region of the adenoviral genome and further comprising the p53 gene under control of a promoter such as SV40 and operably linked to a polyA site from SV40 because Berkner teaches that these elements are standard in the generation of adenoviral vectors. It would have been obvious for the ordinary skilled artisan to do this because the first generation adenoviral vectors (i.e. heterologous gene expression cassettes inserted at the deleted E1 region of the adenoviral genome, etc.) recited in the claims were the standard vectors used at the time of applicants' invention (See Berkner). Given the teachings of the prior art and applicants' claims, it must be assumed that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 9-13 and 22-26 and 28-72 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-32 and 34-35 of copending Application No. 08/626,678 (hereafter the '678 application) in view of Berkner (cited above). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the '678 application recite pharmaceutical compositions comprising recombinant adenoviral vectors capable of expressing the p53 gene, wherein said pharmaceutical compositions are designed to be administered to humans for treatment of cancer (as per the instant claims). It would have been obvious to the ordinary skilled artisan to use the pharmaceutical compositions claimed in the '678 application in methods of treating cancer since these adenoviral vectors are specifically designed to express a tumor suppressor gene (p53) which inhibits tumorigenicity or causes the death of cancer cells. With regard to the expression cassettes used to drive expression of the p53 gene in the adenoviral vectors, said expression cassettes (i.e. the p53 gene operably linked to the CMV promoter and a polyA sequence and said cassette inserted into the deleted adenoviral E1 region) are recited in the '678 application. The claims in the '678 application do not specifically recite use of SV40 promoters, SV40 polyA sequences, origins of replication, etc. However, Berkner (cited above) recites the use of SV40 promoters, polyA sites, origins of replication, etc. in the context of generating adenoviral vectors for the

expression of heterologous proteins. One of ordinary skill in the art would have been motivated to generate adenoviral vectors with the recited components of the expression cassette because Berkner teaches that these components are standard in the construction of recombinant adenoviral vectors. It would have been obvious to one of ordinary skill in the art to do this because Berkner teaches that use of SV40 polyA sites, promoters, adenoviral origins of replication are standard in the construction of recombinant adenoviral expression vectors. Given the teachings of the claims and prior art, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Terminal Disclaimer filed 7/2/97 is acceptable and has been entered.

Any rejections not repeated in this Office Action are withdrawn.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz, can be reached on (703) 308-1133. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
January 2, 2001

DAVID GUZO
PRIMARY EXAMINER

APPENDIX "C"

EXHIBIT C

PHARMACEUTICAL COMPOSITION CLAIMS

29. A pharmaceutical composition comprising:

(a) a recombinant adenovirus which carries an adenovirus vector construct comprising an expression region encoding p53 under the control of a cytomegalovirus IE promoter; and

(b) a pharmaceutically acceptable carrier, excipient or diluent.

30. The pharmaceutical composition of claim 29, wherein said vector construct further comprises a polyadenylation signal.

31. The pharmaceutical composition of claim 30, wherein said recombinant adenovirus is replication deficient.

32. The pharmaceutical composition of claim 31, wherein said vector construct lacks the E1A and E1B regions.

34. The pharmaceutical composition of claim 32, wherein said expression region replaces said E1A and E1B regions of said vector construct.

35. The pharmaceutical composition of claim 34, wherein said adenovirus has the genome structure of FIG. 1.

APPENDIX "D"

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/626,678	04/02/96	ZHANG W	INGN:005-1/H

HM12/0711

FULBRIGHT & JAWORSKI L.L.P
600 CONGRESS AVENUE
SUITE 2400
AUSTIN TX 78701

EXAMINER	
GUZO,D	
ART UNIT	PAPER NUMBER
1636	21

DATE MAILED: 07/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/626,678	ZHANG ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-25,27-32 and 34-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-25,27-32 and 34-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The indicated allowability of claims 22-25, 27-32 and 34-42 is withdrawn in view of the newly applied provisional obviousness type double patenting rejections.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 22 and 36-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 67 of copending Application

No. 09/447,681. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim an adenovirus vector with the same component parts, e.g. a p53 gene under control of a CMV promoter. The claims differ in that claim 67 in the '681 application recites a wild type p53 gene while the instant claims recite a p53 encoding region. However, the claimed limitation in the instant case is broader in scope and totally encompasses the '681 limitation. Therefore, the instant claims if allowed would provide patent protection to adenoviral vectors encompassing p53 genes not claimed in the '681 application. Also, if a patent resulting from the instant claims was issued and transferred to a assignee different from the assignee holding a patent issuing on the '681 application, then two different assignees would hold a patent to the claimed adenoviral vectors and thus improperly there would be possible harassment by multiple assignees. With regard to the CMV promoter, it is noted that the CMV IE promoter is one of the most widely used standard promoters for directing expression of heterologous nucleic acid sequences in eukaryotic cells and would have been the obvious CMV promoter for use in recombinant vectors such as adenoviral vectors. The ordinary skilled artisan would have been motivated to use the CMV IE promoter because it has been shown to function in most eukaryotic cells and was one of the most well known and widely used promoters in recombinant expression constructs. With regard to the cell recited in claim 36, it is noted that the adenoviral vector recited in the '681 application is designed to be used to infect cells and indeed, is useless until it infects a host cell. Give the teachings of the claim in the '681 application and given the level of skill of the ordinary skilled artisan at the time the invention was made, it must be

considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Claims 22-25, 27-28 and 36-42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-26 and 29-34 of copending Application No. 09/668,532. Although the conflicting claims are not identical, they are not patentably distinct from each other because the adenoviral DNA segments recited in the '532 application are expression vectors which comprise the same elements as recited in the instant claims and because the DNA segments recited in the '532 application are designed to be packaged into adenoviral particles (as explicitly recited in claim 34 of the '532 application). The only difference between the two sets of claims in terms of components of the adenoviral DNA constructs involves the CMV promoter. The ordinary skilled artisan seeking to choose a CMV promoter to incorporate into the recited adenoviral expression constructs would have been motivated to choose the CMV IE promoter since this promoter is one of the most well known and widely used promoters in recombinant expression constructs. It would have been obvious for the ordinary skilled artisan to do this because the CMV IE promoter is one of the most commonly used promoters in recombinant expression constructs and would have been the most obvious CMV promoter to use in generating the instant recombinant constructs. With regard to the cell

recited in claim 36 of the instant application, it is noted that the adenoviral vector constructs are designed to be introduced into target cells and indeed, are cannot express the p53 gene unless they are introduced into target cells. Given the claims in the '532 application and the level of skill in the art at the time the invention was made, it must be assumed that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 29-32 and 34-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9, 13, 22, 23, 24, 25, 27, 28, 36, 56-59 and 63 of copending Application No. 08/459,713. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims recite pharmaceutical compositions comprising a recombinant adenovirus containing a adenovirus vector construct comprising a p53 coding region inserted into a deleted E1a-E1b region (map units 1.3 to 9.2 of Ad5 as shown in Fig. 1) followed by a polyA signal and under control of a E1 enhancer. The instant pharmaceutical compositions are designed to be used in methods of treating cancers in patients by replacing defective p53 coding regions with the p53 coding regions contained in the adenoviral vector. It would have been obvious for the ordinary skilled artisan to use the instantly claimed pharmaceutical compositions in the methods of treating cancers recited in the '713 application because said pharmaceutical compositions are designed to

treat cancer by introducing normal p53 coding regions to cancer cells which lack a normal p53 gene. The ordinary skilled artisan would have been motivated to do this because the pharmaceutical compositions recited in the instant application are designed to treat cancers resulting from defective p53 genes by introducing normal p53 genes into the cancer cells. Given the claims in the '713 application and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Robert Schwartzman, can be reached on (703) 308-7307. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

DAVID GUZO
PRIMARY EXAMINER

David Guzo
July 9, 2001

APPENDIX "E"

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on the date below:

October 11, 2001
Date

Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Zhang et al.

Serial No.: 08/626,678

Filed: April 2, 1996

For: RECOMBINANT P53 ADENOVIRUS METHODS AND COMPOSITIONS

Group Art Unit: 1636

Examiner: Guzo, D.

Atty. Dkt. No.: INRP:005--1/GNS

RESPONSE TO OFFICE ACTION DATED JULY 11, 2001

Commissioner for Patents
Washington, D.C. 20231

Commissioner:

This paper is submitted in response to the Office Action dated July 11, 2001 for which the three-month date for response is October 11, 2001.

It is believed that no fee is due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10012303/GNS.

Reconsideration of the application is respectfully requested.

RESPONSE TO OFFICE ACTION

There are three provisional obviousness-type double patenting rejections of the claims.

A. **Rejection of Claims Based on Copending Application No. 08/459,713**

The Action provisionally rejects claims 29-32 and 34-35 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9, 13, 22, 23, 24, 25, 27, 28, 36, 56-59, and 63 of copending Application No. 08/459,713 ("the '713 application"). Applicants traverse this rejection.

In the parent application (Application No. 08/145,826 ("parent application")) of both the present application and the '713 application, there was an Office Action mailed June 3, 1994 that contained a three-way restriction (Appendix A). Claims drawn to recombinant adenovirus (Group I) were restricted from claims drawn to methods of restoring p53 (Group II). The '713 application was filed as a divisional application with claims directed to methods of restoring. The Action indicates that the basis for the obviousness-type double patenting rejection are claims in the '713 application that are directed to methods of treating (amended from "method of restoring"), which are Group II claims. In the present application, which was filed as a continuation of the parent application, the claims are directed to "a recombinant adenovirus" and a "pharmaceutical composition comprising a recombinant adenovirus," which are more closely related to the Group I claims than to the Group II claims.

Because the rationale for originally restricting the Group I claims from the Group II claims has similar applicability to the present case, a double patenting rejection of similar adenovirus claims in the instant case with respect to the '713 application seems inappropriate under 35 U.S.C. § 121 and as explained in MPEP § 804.01. Accordingly, Applicants respectfully request this rejection be withdrawn on this ground.

B. Rejection Based on Copending Application Nos. 09/447,681 and 09/668,532

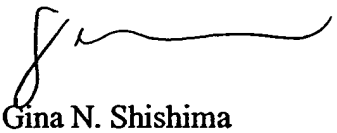
Claims 22 and 36-37 were provisionally rejected over claim 67 in copending Application No. 09/447,681. Claims 22-25, 27-28, and 36-42 were also provisionally rejected over claims from copending Application No. 09/668,532. Applicants will submit a terminal disclaimer, if appropriate, with respect to these applications once all the instant claims are otherwise in condition for allowance.

C. Conclusion

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants earnestly solicit favorable reconsideration of the pending claims.

The Examiner is invited to contact the undersigned attorney at (512) 536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Gina N. Shishima
Reg. No. 45,104
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: October 11, 2001

APPENDIX "F"

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/626,678	04/02/1996	WEI-WEI ZHANG	INGN:005-1/H	8120

7590 01/03/2002

FULBRIGHT & JAWORSKI L.L.P
600 Congress Avenue
Suite 2400
Austin, TX 78701

EXAMINER
GUZO, DAVID

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

RECEIVED
Date(s) Docketed: 3/3/02 Resp. to Double Advisory Action; 4/3/02 Resp. to Final OA/Not. of Appeal Due; 4/3/02 final deadline
JAN 10 2002
Client: INRP: 005--1
Attorney(s): SLH/GNS
Initials: KM 10012303

Office Action Summary	Application No.	Applicant(s)	
	08/626,678	ZHANG ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-25,27-32 and 34-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-25,27-32 and 34-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Applicants' Copy

Form PTO-1449 (modified)	Atty. Docket No. INRP:005–1/GNS	Serial No. 08/626,678
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant Wei-Wei Zhang and Jack A. Roth	
	Filing Date: April 2, 1993	Group: 1636

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name	Class	Sub Class	Filing Date of App.
	A1						

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Class	Sub Class	Translation Yes/No
JZ	B18	WO 93/25224	12/23/93	PCT	—		
JZ	B19	WO 94/06910	3/31/94	PCT	—		
JZ	B20	04-009338	1/14/92	Japan	—		

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C1	

25059084.1

EXAMINER: David Zuzo	DATE CONSIDERED: 12/29/01

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

DETAILED ACTION

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 22 and 36-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 67 of copending Application No. 09/447,681. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim an adenovirus vector with the same component parts, e.g. a p53 gene under control of a CMV promoter. The claims differ in that claim 67 in the

'681 application recites a wild type p53 gene while the instant claims recite a p53 encoding region. However, the claimed limitation in the instant case is broader in scope and totally encompasses the '681 limitation. Therefore, the instant claims if allowed would provide patent protection to adenoviral vectors encompassing p53 genes not claimed in the '681 application. Also, if a patent resulting from the instant claims was issued and transferred to a assignee different from the assignee holding a patent issuing on the '681 application, then two different assignees would hold a patent to the claimed adenoviral vectors and thus improperly there would be possible harassment by multiple assignees. With regard to the CMV promoter, it is noted that the CMV IE promoter is one of the most widely used standard promoters for directing expression of heterologous nucleic acid sequences in eukaryotic cells and would have been the obvious CMV promoter for use in recombinant vectors such as adenoviral vectors. The ordinary skilled artisan would have been motivated to use the CMV IE promoter because it has been shown to function in most eukaryotic cells and was one of the most well known and widely used promoters in recombinant expression constructs. With regard to the cell recited in claim 36, it is noted that the adenoviral vector recited in the '681 application is designed to be used to infect cells and indeed, is useless until it infects a host cell. Give the teachings of the claim in the '681 application and given the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants, in the response filed 10/18/01, do not traverse this rejection but instead indicate that they will submit a Terminal disclaimer, if appropriate, upon indication of allowable subject matter. The rejection is therefore maintained.

3. Claims 22-25, 27-28 and 36-42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-26 and 29-34 of copending Application No. 09/668,532. Although the conflicting claims are not identical, they are not patentably distinct from each other because the adenoviral DNA segments recited in the '532 application are expression vectors which comprise the same elements as recited in the instant claims and because the DNA segments recited in the '532 application are designed to be packaged into adenoviral particles (as explicitly recited in claim 34 of the '532 application). The only difference between the two sets of claims in terms of components of the adenoviral DNA constructs involves the CMV promoter. The ordinary skilled artisan seeking to choose a CMV promoter to incorporate into the recited adenoviral expression constructs would have been motivated to choose the CMV IE promoter since this promoter is one of the most well known and widely used promoters in recombinant expression constructs. It would have been obvious for the ordinary skilled artisan to do this because the CMV IE promoter is one of the most commonly

used promoters in recombinant expression constructs and would have been the most obvious CMV promoter to use in generating the instant recombinant constructs. With regard to the cell recited in claim 36 of the instant application, it is noted that the adenoviral vector constructs are designed to be introduced into target cells and indeed, are cannot express the p53 gene unless they are introduced into target cells. Given the claims in the '532 application and the level of skill in the art at the time the invention was made, it must be assumed that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants, in the response, filed 10/18/01, do not traverse this rejection but instead indicate that a Terminal Disclaimer will be submitted, if appropriate, upon indication of allowable subject matter. The rejection is therefore maintained.

4. Claims 29-32 and 34-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9, 13, 22, 23, 24, 25, 27, 28, 36, 56-59 and 63 of copending Application No. 08/459,713. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims recite pharmaceutical compositions comprising a recombinant adenovirus containing a adenovirus vector construct comprising a p53 coding region inserted into a deleted

E1a-E1b region (map units 1.3 to 9.2 of Ad5 as shown in Fig. 1) followed by a polyA signal and under control of a E1 enhancer. The instant pharmaceutical compositions are designed to be used in methods of treating cancers in patients by replacing defective p53 coding regions with the p53 coding regions contained in the adenoviral vector. It would have been obvious for the ordinary skilled artisan to use the instantly claimed pharmaceutical compositions in the methods of treating cancers recited in the '713 application because said pharmaceutical compositions are designed to treat cancer by introducing normal p53 coding regions to cancer cells which lack a normal p53 gene. The ordinary skilled artisan would have been motivated to do this because the pharmaceutical compositions recited in the instant application are designed to treat cancers resulting from defective p53 genes by introducing normal p53 genes into the cancer cells. Given the claims in the '713 application and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants traverse this rejection by asserting that given the restriction made in the parent of the '713 application, given the prosecution of treatment claims in the '713 applicant and given the instant claims reading on recombinant adenoviruses and pharmaceutical compositions comprising

recombinant adenoviruses, it would appear that a double patenting rejection against the claims in the '713 application is not warranted.

5. Applicant's arguments filed 10/18/01 have been fully considered but they are not persuasive. It is noted that the double patenting rejection is not being made against any of the instant claims which recite recombinant adenoviruses. The rejection is being made against claims reciting a "pharmaceutical composition". A pharmaceutical composition is distinct in that it is a composition which is a medicament or which has a therapeutic benefit for a patient. The instant claims reading on "pharmaceutical compositions" are therefore more related to the Group II claims in the parent of the '713 application. Clearly, the instantly claimed pharmaceutical compositions comprising recombinant adenoviruses capable of expressing wild-type p53 are obvious over claims (pending in the '713 application) reading on a method of treating cancers in patients comprising administering pharmaceutical compositions comprising recombinant adenoviruses capable of expressing wild-type p53 because the method claims (in the '713 application) merely recite the intended use of the instantly claimed pharmaceutical compositions.

No Claims are allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Responses can be faxed directly to the examiner at (703) 746-5061.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

David Guzo
December 29, 2001

DAVID GUZO
PRIMARY EXAMINER

APPENDIX "G"

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date below:

12/10/04
Date

Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Roth

Serial No.: 09/447,681

Filed: November 23, 1999

For: ADENOVIRUS p53 COMPOSITIONS AND METHODS

Group Art Unit: 1632

Examiner: Crouch, Deborah

Atty. Dkt. No.: INRP:003--2

SECOND DECLARATION OF LOUIS ZUMSTEIN, PH.D

UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Louis Zumstein, Ph.D., declare the following:

1. I am the Director of Research at Introgen Therapeutics, Inc. ("Introgen") in Houston, Texas.

2. I understand that the vector referred to as AdCMVp53 in the Examples of USN 08/145,826 is the vector referred to as INGN 201 by Introgen (now marketed as "Advexin").

3. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or

imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

8-December-2004

Date

Louis Zumstein, Ph.D.